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# Chiral-at-Ruthenium Catalyst with Sterically Demanding Furo[3,2-b]pyridine Ligands

Tianjiao Cui,[a] Jie Qin,[a] Klaus Harms,[a] and Eric Meggers*[a]

Dedication ((optional))

**Abstract:** A sterically demanding derivative of a previously introduced chiral-at-metal ruthenium(II) catalyst scaffold is introduced. It is composed of two bidentate furo[3,2-b]pyridyl functionalized *N*-heterocyclic carbene ligands. Their *cis*-coordination generates helical chirality and a stereogenic ruthenium center. Two additional labile acetonitriles compose the catalytic site which is highly shielded by two 2-(*tert*-butyl)furo[3,2-b]pyridine moieties. The synthesis of the non-racemic ruthenium catalyst and its catalytic properties for the enantioselective alkynylation of 2,2,2-trifluoroacetophenone and pentafluorobenzaldehyde are reported and compared with sterically less demanding derivatives.

## Introduction

Chiral transition metal complexes are an important class of asymmetric catalysts and typically synthesized by reacting metal salts or organometallic precursors with carefully tailored chiral ligands.[2] Recently, an alternative design strategy has emerged in which the overall chirality is the consequence of the asymmetric coordination of exclusively achiral ligands around a central metal, thereby implementing metal-centered chirality.[3-11] Such complexes have been dubbed “chiral-at-metal” to indicate that the overall chirality formally originates from a stereogenic metal center in order to distinguish this design approach from conventional chiral transition metal complexes, which frequently also possess metal-centered chirality but induced by the chiral ligand sphere.[12-14] This chiral-at-metal approach has the appeal of structural simplicity. More importantly, without the requirement of chiral motifs in the ligand sphere, untapped opportunities emerge for the design of novel catalyst architectures with potentially novel overall properties.

We recently introduced chiral-at-ruthenium asymmetric catalysts bearing two configurationally stable bidentate *N*-(2-pyridyl)-substituted *N*-heterocyclic carbene (PyNHC) ligands in addition to two labile acetonitriles (Figure 1).[15,16] With all ligands being achiral, the helical arrangement of the two *cis*-coordinated bidentate PyNHC ligands provides a metal-centered Λ- (left-handed screw sense) or Δ-configuration (right-handed screw sense). The complexes **Ru1** and **Ru2** were demonstrated to be excellent catalysts for the enantioselective alkynylation of trifluoromethyl ketones including an application to the enantioselective synthesis of key propargyl alcohol intermediates of the anti-HIV drug efavirenz.[15,17] Here we report the synthesis and catalytic properties of the sterically more demanding chiral-at-ruthenium catalysts **Ru3** in which we replaced the two pyridines with 2-(*tert*-butyl)furo[3,2-b]pyridine moieties. This creates a more extended propeller with high steric crowding around the catalytic site near the two exchange-labile acetonitrile ligands. We show that this steric crowding has a profound influence on catalytic activity and enantioselectivity.

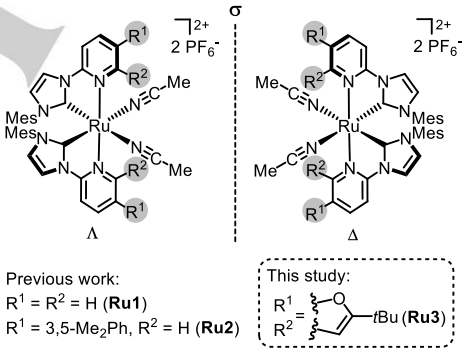


**Figure 1.** Previous designs and this work regarding chiral-at-metal ruthenium catalysts.

## Results and Discussion

The multistep synthesis of the imidazolium ligand **1** is shown in the Supporting Information. Reaction of $RuCl_3$ hydrate with **1** in ethylene glycol at 200 °C followed by treatment with $AgPF_6$ provided the racemic complex *rac*-**Ru3** in 66% yield (Scheme 1). Reaction of this racemic complex with the salicyloxazoline (*S*)-**2** under basic conditions afforded the complex Λ-(*S*)-**3** as a single diastereomer in 34% yield. Likewise, reaction of *rac*-**Ru3** with the salicyloxazoline (*R*)-**3** provided the enantiomeric complex Δ-(*R*)-**3** in 30% yield. A crystal structure of Λ-(*S*)-**3** is shown in Figure 2 and establishes the relative and abolute configuration of this intermediate. Treatment of this complex and its enantiomer with TFA in MeCN followed by anion metathesis with $NH_4PF_6$ provided the complexes Λ-**Ru3** (54% yield) and Δ-**Ru3** (44% yield) as single enantiomers.

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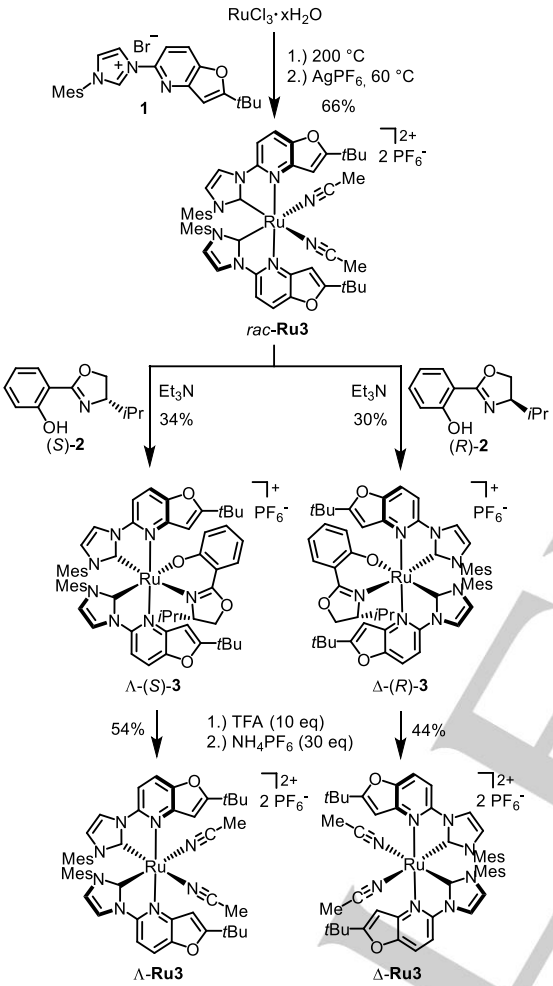
Supporting information for this article is given via a link at the end of the document.

The Λ-enantiomer of a crystal structure of *rac*-**Ru3** is shown in Figure 3 and reveals an undistorted octahedral coordination sphere around the stereogenic ruthenium center with the two mesityl groups stacking with the fura[3,2-b]pyridine heteroaromatic ligands. The $C_2$-symmetric complex shows a helical, propeller-type arrangement of the two bidentate ligands. The ruthenium center at the two labile acetonitrile ligands, which constitutes the catalytic site, is significantly shielded by the two 2-(*tert*-butyl)fura[3,2-b]pyridine moieties.




**Scheme 1.** Synthesis of the enantiomerically pure chiral-at-metal ruthenium complexes Λ- and Δ-**Ru3**.

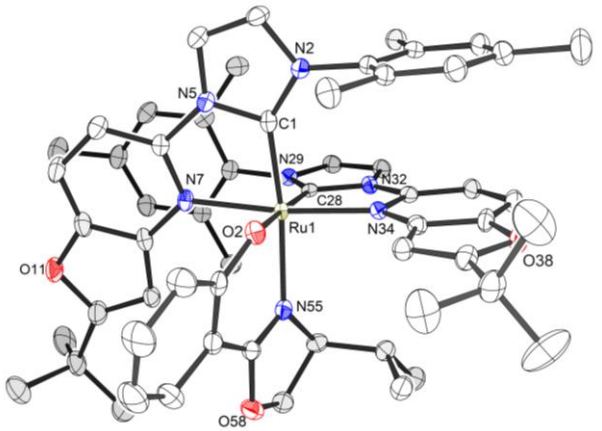



**Figure 2.** X-ray structure of Λ-(*S*)-**3**. ORTEP drawing with 50% probability thermal ellipsoids. Solvent and counterion are omitted for clarity.

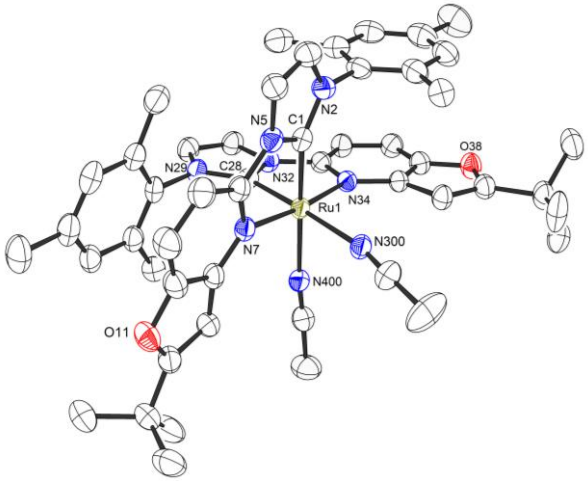
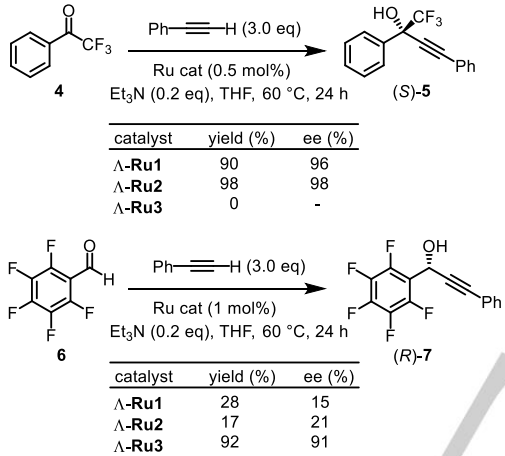



**Figure 3.** X-ray structure of *rac*-**Ru3**. Only the Λ-enantiomer is shown. ORTEP drawing with 50% probability thermal ellipsoids. Solvent and counterion are omitted for clarity.

Next, we investigated the catalytic properties of this chiral-at-ruthenium catalyst. Complexes **Ru1** and **Ru2** were recently demonstrated to be excellent catalysts for the enantioselective alkynylation of trifluoromethyl ketones.[15,17,18] We therefore used the reaction of 2,2,2-trifluoroacetophenone (**4**) with phenylacetylene as a first model reaction. Interestingly, whereas Λ-**Ru1** or Λ-**Ru2** at a catalysts loading of 0.5 mol% in the presence of catalytic amounts of the base $Et_3N$ at 60 °C provided the propargylic alcohol (*S*)-**5** with high yields and high enantioselectivities, no reaction occured with the fura[3,2-b]pyridine complex Λ-**Ru3** (Scheme 2). We attribute this to the high steric hindrance induced by the two 2-(*tert*-butyl)fura[3,2-b]pyridine moieties. A computational study by Houk and coworkers on this enantioselective alkynylation of trifluoromethyl ketones catalyzed by such chiral-at-ruthenium complexes support a mechanism with an inner-sphere acetylide transfer from an intermediate ruthenium acetylide to the ruthenium-coordinated trifluoromethyl ketone through a highly compact four-membered transition state.[19] The requirement in this catalytic mechanism for a simultaneous binding of both

substrates to the ruthenium center apparently leads to a significant steric crowding and a high sensitivity to additional steric effects which might explain the diminished catalytic activity of **Ru3** for this transformation.

Due to these disappointing results we turned our attention to aldehydes as sterically less demanding substrates for an enantioselective alkynylation. As our model reaction we chose the alkynylation of pentafluorobenzaldehyde (**6**) with phenylacetylene. Interestingly, when performed in the presence of 1.0 mol% ruthenium catalysts, 0.2 equivalents of $Et_3N$ at 60 °C, Λ-**Ru1** and Λ-**Ru2** provided the propargylic alcohol (*S*)-**7** with only low yields and low enantioselectivities. In contrast, the fura[3,2-b]pyridine complex Λ-**Ru3** afforded (*S*)-**7** in a yield of 92% and with 91% ee under identical reaction conditions.[20] For aldehyde **6**, the high steric hindrance of Λ-**Ru3** is an advantage and leads to a higher yield and higher enantioselectivity of the alkynylation product.




| catalyst | yield (%) | ee (%) |
|---|---|---|
| Λ-**Ru1** | 90 | 96 |
| Λ-**Ru2** | 98 | 98 |
| Λ-**Ru3** | 0 | - |

| catalyst | yield (%) | ee (%) |
|---|---|---|
| Λ-**Ru1** | 28 | 15 |
| Λ-**Ru2** | 17 | 21 |
| Λ-**Ru3** | 92 | 91 |

**Scheme 2.** Catalytic enantioselective alkynylations.

## Conclusions

We here introduced a new member of the family of chiral-at-metal ruthenium catalysts composed of two *cis*-coordinated bidentate *N*-(2-pyridyl)-substituted *N*-heterocyclic carbene ligands in addition to two acetonitriles. The $C_2$-symmetric catalyst features a helical arrangement of the two achiral bidentate ligands with a formal stereogenic ruthenium center. The two 2-(*tert*-butyl)fura[3,2-b]pyridine moieties generate a significant steric crowding at the site of catalysis which strongly affects the catalytic activity and asymmetric induction. The photochemical properties of this and related complexes are currently under investigation.

## Experimental Section

Experimental details, analytical data, crystallographic data and structure refinement statistics are provided in the Supporting Information. CCDC 1876633 and 1876632 contains the supplementary crystallographic data for the structures of Λ-(*S*)-**3** and *rac*-**Ru3**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

**Asymmetric catalysis procedure**: The reaction **6** → (*R*)-**7** catalyzed by Λ-**Ru3** is provided as a representative example. A dried Schlenk tube (10 mL) was charged with Λ-**Ru3** (2.4 mg, 0.002 mmol) and pentafluorobenzaldehyde (39.2 mg, 0.20 mmol) in THF (0.50 mL). The tube was purged with nitrogen, and $Et_3N$ (5.6 μL, 0.04 mmol) was added via syringe, followed by the addition of phenylacetylene (61.3 mg, 0.60 mmol). The vial was sealed and the reaction stirred at 60 °C for 24 h under an atmosphere of nitrogen. Then, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/*n*-hexane = 1:50) to afford the propargylic alcohol (*S*)-**7**.[20] $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.42 – 7.33 (m, 2H), 7.26 (dtd, *J* = 7.2, 5.5, 5.0, 2.1 Hz, 3H), 5.90 (d, *J* = 8.0 Hz, 1H), 2.61 (d, *J* = 8.0 Hz, 1H). Enantiomeric excess was established by HPLC analysis using a Daicel Chiralcel AS-H column. (HPLC conditions: UV-detection at 254 nm, mobile phase *n*-hexane/isopropanol = 95:5, flow rate 1.0 mL/min, column temperature 25 °C, $t_R$ (major) = 7.7 min, $t_R$ (minor) = 12.5 min).

## Acknowledgements

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**Keywords:** chiral-at-metal • metal-centered chirality • ruthenium • fura[3,2-b]pyridine• alkynylation

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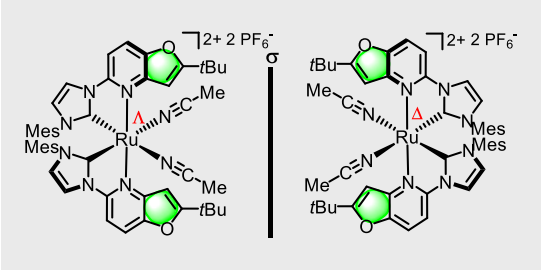
# COMMUNICATION




**Chiral catalyst**

*T. Cui, J. Qin, K. Harms, E. Meggers**

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**Chiral-at-Ruthenium Catalyst with Sterically Demanding Furo[3,2-b]pyridine Ligands**

A chiral-at-metal ruthenium catalyst composed of two *cis*-coordinate N-(furo[3,2-b]pyridyl)-substituted N-heterocyclic carbene ligands in addition to two acetonitriles is introduced. The two 2-(*tert*-butyl)fura[3,2-b]pyridine moieties generate a high steric crowding at the site of catalysis which affects both catalytic activity and asymmetric induction.